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DTPa Hib Combination Vaccines: Population-Based Evaluation of Vaccine Effectiveness-results after 18 months of surveillance

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In 1995 we had reported that DTPa Hib-combination vaccines produce mean anti-Hib-PRP antibody concentrations that are lower than those following separate administration of Hib vaccines (1, 2). While many experts believe that concerns over this finding are unwarranted (3), the clinical implication of lower anti-Hib-antibody concentrations has not yet been shown. In Germany, DTPa-based Hib-combination vaccines were introduced in late 1996 and have now reached a market-share of 92%. This study used this unique situation to investigate the incidence of invasive *H. influenzae* (Hi) disease in Germany and to calculate vaccine effectiveness.

A case of invasive Hi disease was defined as a child hospitalized with illness clinically compatible with invasive Hi disease and isolation of Hi from a normally sterile body site. (Note: In Germany, there is a strict separation between hospital and outpatient pediatricians and as a result all children with invasive Hi disease including bacteremia are treated in hospitals). Invasive Hi disease was actively surveyed using independent hospital and laboratory based surveillance systems.

The "**E**rhebungseinheit für **S**eltene **P**ädiatrische **E**rkrankungen in Deutschland (ESPED) ("clinical registration system for rare pediatric diseases" in Germany) operates under the auspices of the German Society for Pediatrics. The laboratory system (laboratory ESPED) is based at the Robert-Koch-Institute, Berlin. Postcards soliciting the admission of any child with one of up to twelve rare diseases are sent monthly to the chiefs of all pediatric hospital departments. Likewise, all chiefs of microbiology are asked if their laboratory cultured Hi from a normally sterile body site. Additional information from each case, including vaccination history, was sought by calling the hospital pediatricians asking for copies of the vaccination card and the hospital discharge letter.

The vaccination coverage in Germany during the study period was documented by an established random-digit dialing method.
In this ongoing study, 74 Hi-cases (including 36 type b) were documented by both ESPED systems in the period from 01/98-06/99. This represents a continued decline in the numbers of invasive Hi cases in Germany compared to previous studies. Vaccine effectiveness calculations were restricted to "age-eligible children" i.e. any child who was at least 2 months old and young enough to have received a DTaP-based Hib-combination vaccine (all children born after June 1, 1996). Of the 37 age-eligible children with invasive Hi disease, 24 were due to Hib, 8 were not typed, and 5 were typed as non-b. In the 32 age-eligible children with Hib or untyped Hi, 15 children had received no vaccine and 17 had received at least 1 dose of a Hib-conjugate vaccine. Eight children had received at least one dose of an acellular pertussis-Hib combination vaccine. None of these children had received a complete vaccination course as recommended (i.e. a full 3 dose primary series in the 1st year of life and a booster in the 2nd year). For children having received a full 3 dose primary vaccination series with SB-DTPa/Hib-vaccine and SB-DTPa-IPV/Hib-vaccine (data for other DTPa-Hib combination vaccines can not be given due to a low vaccination rate with these vaccines) vaccine effectiveness was 99.3% (95% CI: 98.9-99.53. In comparison, the effectiveness of 2 doses of PRP-D vaccine was significantly lower. Using capture-recapture technique to calculate the true incidence of invasive Hi disease in Germany from the two independent reporting systems the estimated number is 83.

In conclusion, ESPED is a reliable reporting system which documents a continuing decline of invasive Hi disease in Germany, where DTaP-based Hib-combinations have a more than 80% market share. In a birth cohort of approximately 800,000 children annually, vaccine effectiveness of a primary vaccination series with SB-DTaP-based Hib combinations was more than 99% for three doses, whereas the monovalent PRP-D-vaccine had a significantly lower effectiveness. Thus, the lower anti-Hib-PRP antibody concentrations mentioned above have no clinical relevance.

Literature

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